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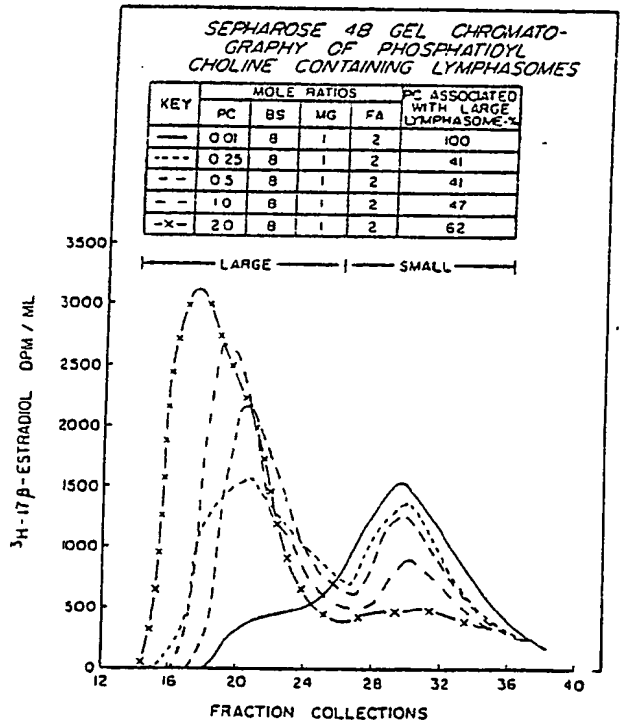
(54) Title: MICELLULAR DRUG DELIVERY SYSTEM

(57) Abstract

A xenobiotic delivery composition comprising lipid micellular particles incorporating the xenobiotic. The lipid micellular particles comprise a bile acid or the pharmaceutically acceptable salts thereof, a fatty acid and a monoglyceride. Methods of delivering the xenobiotic composition are also set forth in this invention.



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MICELLULAR DRUG DELIVERY SYSTEM

This invention relates to the delivery and release of xenobiotics within a mammalian host. More particularly, it relates to a xenobiotic delivery composition on the form of lipid micelles and to a method of delivering xenobiotics to a mammalian host which predetermines and controls the pharmacodynamics of the xenobiotic as delivered and released.

In many different situations and under many varied circumstances it is desirable to introduce into a mammalian host pharmacologically active agents which are foreign to the host, these agents hereinafter being termed "xenobiotics." These xenobiotics include, but are not necessarily limited to, drugs, diagnostic agents, blood substitutes endogenous biological compounds, hormones, immunological adjuvants and the like.

In the administration of any xenobiotic a certain degree of specificity must be attained, and specificity requires that the xenobiotic reach its target selectively and controllably. The absence of specificity associated with the use of many xenobiotics can thus deprive them of an appreciable part, if not essentially all, of their potential effectiveness in attaining the results desired from their use. For example, a chemotherapeutic drug which cannot be retained by blood plasma for a time sufficient for an appreciable amount of the drug to reach the target tissue or an orally administered drug which is destined for the blood stream but which cannot pass through the gastrointestinal

tract lacks the degree of specificity which could make it highly effective. Thus in lacking the desired specificity, a xenobiotic may exhibit essentially none or only a limited degree of the pharmacodynamics desired to realize its full potential. Among such pharmacodynamics may be listed plasma kinetics, tissue distribution, degree of toxicity, levels of therapeutic drugs in vivo, solubility of xenobiotics normally incompatible with other pharmaceutical formulations, and metabolic activation of the xenobiotics.

In the prior art it has been recognized that it would be desirable to beneficially alter and control the specificity or pharmacodynamics of many of the xenobiotics found to have desirable properties. One prior art approach to controlling the specificity of drugs involves the use of implant devices located, normally through a surgical procedure, in or near the organ to which the drug is to be delivered. Typically, these implant devices comprise a covalent matrix material containing the drug to be delivered. These matrix materials may be water-soluble (e.g., carboxymethyl cellulose or polyvinyl alcohol), water-swellable (e.g., hydrogels or gelatin), hydrolytic polymers (e.g., polylactic acids, polyglycolic acids or poly-α-amino acids), or nonhydrolytic polymers (e.g., organopolysiloxane rubber). Generally, although these implant devices can control the rate at which the drug they contain can be delivered through diffusion or hydrolysis, they can exercise little if any alteration of the pharmacodynamics of the drug released. In addition, the drug implant method requires the attention of

skilled surgeons and support staff in order to effectively and safely utilize the device. As such, primary consideration for administration of xenobiotics has been directed to the more facile oral delivery techniques and carriers for accomplishing such techniques.

One method which has been used to increase the effectiveness of orally administered substances is to increase their absorption area by reducing their particle size. Particle size has been shown to be critical for orally administered steroids spironolactone, and griseofulvin. Estradiol, the primary estrogenic hormone, has shown promising pharmacological activity when administered orally and micronized estradiol was clinically effective in a preliminary study of menopausal therapy and was well tolerated. A recent study has shown that micronized estradiol was readily absorbed from the gastrointestinal tract; however, the serum concentrations of estrone rather than estradiol were markedly increased. This finding indicates that orally absorbed estradiol is rapidly metabolized. The gastrointestinal mucosa, rather than the liver may be the primary site of this extensive metabolism of orally administered estradiol.

In addition to reducing particle size, the efficacy of certain drugs given orally has been improved by administering them in oil solutions. As used throughout the specification, oils refers to the high molecular weight glycerol esters of fatty acids principally of vegetable origin. For example, the absorption of both regular and micronized griseofulvin are somewhat enhanced if co-admin-

istered with meals high in fat or triglyceride content or in an oil and water emulsion. Testosterone undecanoate dissolved in arachis (peanut) oil is more biologically active than the micro-crystal suspension in water possibly due to absorption of testosterone undecanoate via the lymph rather than the portal system. Similarly, the pathway of absorption of orally administered ethynyl estradiol-3-cyclopentyl ether was influenced by the vehicle of administration.

Central to the numerous investigations of the mechanism of fat absorption has been the basic question as to the chemical nature of the fats which gain entrance to the mucosal cells. Triglycerides are by far the most important lipids in the diet and the chemical composition of the natural triglycerides vary considerably in their fatty acid composition and in their positional conformation. For example, the content of palmitate, oleate, and linoleate varies among the common seed oils; corn (13, 29 and 54%, respectively), peanut (6, 61 and 22%), respectively), and palm (48, 38 and 9%, respectively). The digestion of triglycerides requires the enzyme, pancreatic lipase, and bile salts. This enzyme demonstrated a preferential hydrolysis of the 1 and 3 positions of the triglyceride to give the final products a 2-monoglyceride and fatty acids. Enzymatic hydrolysis of these triglycerides is incomplete and slow.

It has been shown that conjugated bile salts in the intestine form complexes termed "micelles" with fatty acids

and monoglycerides. Micelles, as used in the prior art and herein are defined as lipid particles of 40-100Å in diameter that to the naked eye appear as clear (rather than milky) solutions, i.e., while oil in water, because of their very small particle size, they appear as solutions. Thus, it appears that a micelle delivery system could provide a novel carrier capable of delivering xenobiotics to very specific regions of the body.

It is therefore a primary object of this invention to provide improved xenobiotic delivery compositions in the form of lipid micelles capable of being readily absorbed within the host system. Another object is to provide xenobiotic delivery compositions of the character described which are compatible with a wide variety of xenobiotics including hydrophobic, hydrophilic or a combination of hydrophobic and hydrophilic compounds and which are nontoxic and biocompatible with the host system. A further object of this invention is to provide xenobiotic delivery compositions which are stable over extended periods of storage as well as in their use within the host system and amenable to various techniques of oral administration.

Another object of this invention is to provide xenobiotic delivery compositions capable of predeterminably and beneficially altering and controlling the pharmacodynamics of the xenobiotic delivered and released within the host system. Among the pharmadocynamics thus beneficially altered

and controlled are plasma kinetics, tissue distribution, toxicity, oral absorption, chemotherapeutic ability, metabolism and the like.

It is another primary object of this invention to provide a method of forming xenobiotic delivery compositions, in the form of lipid micelles, capable of circulating within a mammalian host thereby to deliver the xenobiotic at a predetermined site by effecting a predetermined beneficial alteration in the pharmacodynamics of the xenobiotic.

Yet another primary object of this invention is to provide a method for delivering and releasing a pharmaceutically effective amount of a xenobiotic within a mammalian host in a manner to exercise some predeterminable control over the delivery site, thus enhancing the effectiveness of the xenobiotic.

Other objects of the invention will in part be obvious and will in part be apparent hereinafter.

According to one aspect of this invention there is provided a delivery vehicle incorporating a xenobiotic and being biocompatible with a mammalian host to deliver and release within the aqueous environment of the host the xenobiotic, the pharmacodynamics of which are beneficially altered by reason of its delivery by and release from the vehicle, the delivery composition being in the form of lipid micelles comprising a mixture formed from bile acids and the pharmaceutically acceptable salts thereof, fatty acids and monoglycerides, thereby providing for the controlled release of the xenobiotic therefrom.

According to another aspect of this invention there is provided a method of forming a delivery composition for delivering to and releasing within the aqueous environment of a mammalian host a xenobiotic, the pharmacodynamics of which are predeterminably altered and controlled, comprising the steps of forming lipid micelles of a composition comprising fatty acids and monoglycerides and incorporating the xenobiotic to be delivered within the lipid micelles.

According to yet another aspect of this invention there is provided a method of controllably delivering to and releasing a xenobiotic within the aqueous environment of a mammalian host, comprising the step of introducing into the mammalian host a pharmaceutically effective amount of a xenobiotic contained within lipid micelles formed from a mixture comprising bile acids and the pharmaceutically acceptable salts thereof, fatty acids and a monoglycerides.

According to still another aspect of this invention there is provided a method of predetermining and controlling the pharmacodynamics under which a xenobiotic is delivered within the aqueous environment of a mammalian host, comprising the step of releasing the xenobiotic within the host from lipid micelles formed from a mixture comprising bile acids and the pharmaceutically acceptable salts thereof, fatty acids and monoglycerides, thereby controlling the pharmacodynamics of the xenobiotic.

The invention accordingly comprises the several steps and the relation of one or more such steps with respect

to each of the others, and the composition and article possessing the features, properties, and the relation of constituents, which are exemplified in the following detailed disclosure, and the scope of the invention will be indicated in the claims.

For a fuller understanding of the nature and objects of the invention, reference should be had to the following Figures and the detailed description of the Preferred Embodiments.

Figure 1A. Hydrolysis of U.S.P. corn oil using pancreatic lipase and various mole ratios of bile salts.

Figure 1B. Hydrolysis of U.S.P. corn oil using pancreatic lipase, bile salt: triglyceride ratio of 1:1, and varying the concentration of oil and water.

Figure 1C. Estradiol solubility in the aqueous phase of a triglyceride: water biphase (3:7, w/w) as a function of increasing bile salt: triglyceride ratios.

Figure 1D. Distribution of estradiol in aqueous phase with respect to the hydrolysis of the lipid phase.

Figure 2A. Hydrolysis mixture contained ^{14}C-oleic acid and its monoglyceride, ^{14}C-bile salt and ^{3}H-estradiol.

Figure 2B. Mole percent composition of bile salts, fatty acid and monoglyceride.

Figure 2C. Fatty acid composition of original oil and hydrolyzed oil prior to chromatography and in the monoglyceride fraction following chromatography.

Figure 2D. Fatty acid composition in the fatty acid fraction.

Figure 3A. The recovery of estradiol in lymphasomes, which contained 0 to 2 mole ratios of phosphatidyl choline relative to monoglyceride and which were chromatographed on Sepharose 4B gel columns.

Figure 3B. The size distribution of lymphasomes described in A above.

Figure 3C. The elution pattern of estradiol in phosphatidyl choline containing lymphasomes on Sepharose 4B gel chromatographic columns.

Figure 4A. The time pattern of total estradiol derived radioactivity equivalents in systemic plasma, portal plasma and lymph of surgically prepared dogs that received (^{3}H or ^{14}C) estradiol in a lymphasome preparation.

Figure 4B. The time pattern of identified estradiol equivalents, namely estradiol (E_2) and its glucuronide

(E_2G) and estrone (E_1) and its glucuronide (E_1G) in dog systemic blood.

Figure 4C. The time pattern of identified estradiol, in dog portal blood.

Figure 4D. The time pattern of identified estradiol, in dog lymph.

As used herein, the term "fatty acids" is intended to mean the organic monobasic acids derived from linear or branched hydrocarbons of the formula C_nH_{2n+2} where n is an integer 10 to 24 by the equivalent of oxidation of a methyl group to a carboxylic acid including: saturated fatty acids of the formula $C_nH_{2n-1}COOH$ such illustrated by myristic acid, palmitic acid, stearic acid, etc; monounsaturated fatty acids of the formula $C_nH_{2n-1}COOH$ such illustrated by oleic acid, etc; diunsaturated fatty acids of the formula C_nH_{2n-3}, such illustrated by linolaic acid, etc; and triunsaturated fatty acids of the formula $C_nH_{2n-5}COOH$ such illustrated by linolenic acid, etc.

By the term "monoglyceride" as used herein, is meant the 2-monoesters formed from glycerine and the above defined fatty acids having the general formula $(CH_2)_3(-OH)_2OOCR$ where R is C_{10} to C_{24} alkyl including linear or branched and saturated or mono or polyunsaturated groups.

The term "bile acids" and the pharmaceutically acceptable salts thereof" is intended to mean those naturally

occurring bile acids, such illustrated by cholic acid, deoxycholic acid, lithocholic acid, chenodeoxycholic acid, 3-hydroxy-7ketocholanic acid, etc., their conjugates with the acids glycine and taurine, as well as the nontoxic cationic salts thereof.

The term "lipase" as used herein is defined as any enzyme that changes fats into their component diglycerides, monoglycerides, fatty acids and glycerine. They are typically of natural origin, derived from the liver, pancrease and other digestive organs as well as from a wide variety of plants.

The term "hydrolyzed triglyceride oil" is intended to mean triglycerides, i.e., the above fatty acids forming esters with glycerine, enzymatically hydrolyzed to the above defined monoglycerides, the enzyme being lipase as above defined.

The novel delivery vehicle of the present invention is structured in the form of lipid micelles incorporating a xenobiotic agent. The term "micelles" has heretofore been applied to the form of those products found in the digestive tract (principally the duodenum and jejunum) and known to be a complex of conjugated bile salts with fatty acids and monoglycerides. The lipid micelles of this invention are similar to the naturally occuring micelles but are composed of a synthetic mixture of certain bile acids or the pharmaceutically acceptable salts thereof, monoglycerides and fatty acids. The bile acids preferred in the preparation of this

xenobiotic delivery vehicle are those selected from the group cholic acid, chenodioxycholic acid, dioxycholic acid and lithocholic acid. Particularly preferred are the preferred bile acids conjugated with the acids, glycine or taurine.

While a great variety of monoglycerides can be used in the vehicle of this invention, the preferred monoglycerides are those esters substituted at the 2-position of the three carbon glycerol chain, the substitution being a saturated or unsaturated linear or branched fatty acid having from 10 to 18 carbon atoms in the hydrocarbon chain (including the carboxylate group). Particularly preferred are glycerol laurate, glycerol myristate, glycerol palmitate, glycerol oleate, glycerol linoleate and glycerol linolenate.

As in the case of the monoglycerides described above, the fatty acids finding preferred applicability in this invention are those linear or branched, saturated or unsaturated fatty acids having from 10 to 18 carbon atoms in the hydrocarbon chain (including the carboxylic acid group). Particularly preferred are lauric, myristic, palmitic, oleic, linoleic and linolenic acids.

The delivery vehicle of this invention, composed of the above-disclosed bile acids and the pharmaceutically acceptable salts thereof, monoglycerides and fatty acids in ratios of 10:1:1 , 1:1:10 and 1:10:1, most preferably 2:2:1.

It should be understood that the acid conjugates of the bile acids of this invention are also

capable of forming pharmaceutically acceptable cation salts. These pharmaceutically acceptable cation salts, with respect to the acid moiety as well as the cation salts of the bile acids include for example, the alkali metals, e.g., sodium, potassium, etc.; alkaline earth metals, e.g., calcium, etc; ammonia, organic salts of triethylamine, diethylamine, tris-(hydroxymethyl)aminomethane, ethanolamine, choline, caffeine, and the like.

The term room temperature refers to about 20°C., and all temperatures and temperature ranges refer to degrees centigrade. All percents refer to weight percents and the term equivalent mole amount refers to an amount stoichiometrically equivalent to the other reactant in the reaction referred to.

A further understanding of the invention can be had from the following non-limiting preparation and examples.

PREPARATION I

When xenobiotics are administered in oils and an enchanced absorption of the xenobictic is observed, the oils per se are first enzymatically hydrolyzed, the hydrolylic components are absorbed in the region of the jejunum and subsequently resynthesized into triglycerides prior to their incorporation into chylomicrons. The enzymatic hydrolysis requires pancreatic lipase, bile salts, divalent cations and an alkaline pH. It can be demonstrated that this hydrolysis

is very dependent upon the mole ratio of bile salts and triglycerides (Figure 1A) and the molar concentration of the triglycerides (Figure 1B); that the rate of the enzymatic hydrolysis is slow (Figure 1B and 1D); and that, under less than optimum conditions, the reaction will not go to completion (Figure 1B). Thus it is not surprising that oil per se has not been successful as a xenobiotic-delivery vehicle.

PREPARATION 2

Estradiol-17 , a water insoluble drug, is soluble in triglyceride oils but will partition into an aqueous phase containing bile salts (Figure 1C). Since bile salts are absorbed in the region of the lower ileum, estradiol administered in oil has the potential for partitioning into a bile salt-rich aqueous phase and being absorbed along with bile salts. The partitioning characteristics of estradiol during the process of hydrolyzing triglyceride-oils is shown in Figure 1D). The partioning into the oil-phase following 1 to 3 hours represents large lipid emulsions containing triglycerides, fatty acids, monoglycerides and bile salts. At 4 hours, when most of the triglycerides have been hydrolyzed, the estradiol is associated with the lipid micelle. This hydrolysis mixture was chromatographed on a polyacrylamide gel column (P-10). Chromatography experiments with hydrolysates made from U.S.P. corn oil show that there is no segregation of micelles with respect to fatty acid distrib-

ution. As shown in Figure 2A, [^{3}H]-estradiol co-eluted with the lipid micelles containing hydrolyzed [^{14}C]-triglycerides and [^{14}C]bile salts. The analysis of the column eluates for [^{14}C]-bile salts, ^{14}C-fatty acids and ^{14}C-monoglycerides (Figure 2C) demonstrate that the region corresponding to ^{3}H-estradiol contained more than 2 moles of fatty acids, less than 2 moles of bile salts and approximately 1 mole of monoglycerides. The region where bile salts were enriched did not contain significant concentrations of estradiol. Estradiol in the presence of a hydrolyzed oil phase and excess bile salts aqueous phase partition preferentially to the lipid micelle.

Aliquots from each of these five molar concentrations of estradiol were chromatographed on a polyacrylamide column. The elution profile of the estradiol and the lymphasomes were co-incident; the bile salt-rich micelle region contained minimum amounts of estradiol, even to the point that the lymphasomes were saturated with estradiol. This shows that estradiol solubility in hydrolyzed oil preparations was preferential to that in a bile-salt rich micelle. It was found that estradiol saturation occurred between 0.004 and 0.007 mole percent relative to monoglyceride or triglyceride.

The fatty acid distribution of the fatty acids in both the monoglyceride fraction (Figure 2B) and the fatty acid fraction (Figure 2C) were comparable throughout the column eluates. The monoglyceride fraction (Figure 2B), in

comparison to the fatty acid fraction (Figure 2C), was enriched in linoleic acid (18:2) but it is not further enriched in the region corresponding to the elution of estradiol.

PREPARATION 3

In these Preparations several sources of hydrolyzed triglyceride oils (Table 1) are evaluated. The mole % composition varied somewhat, but the optimum lipid micelle eceluting with estradiol contained approximately 2 moles of fatty acid, 2 moles of bile salts, and 1 mole of monoglycerides (lymphasomes). The fatty acid distribution in the fatty acid and monoglyceride fractions are reflected in the original composition of the triglyceride-oils. Each source of oil for the lymphasome preparations was replicated at least twice for the bioavailability of estradiol in dogs. There was nothing to distinguish any oil as being better than the others. The findings for all lymphasome preparations have been pooled.

EXAMPLE 1

Lymphasome preparations, i.e., containing a molar ratio of bile salt:fatty acid monoglyceride of 2:2:1, are saturated with estradiol at a molar concentration between 0.004 and 0.007 relative to monoglyceride. In preparing

synthetic lipid micelles composed of saturated fatty acids, a greater molar concentration of bile salts is required. When excess bile salts are present, estradiol has the potential of partitioning from the lymphasome into the bilesalt enriched solution (Figure 3A). Since this situation of having excess bile salts along with lymphasome formulations of estradiol exist in the intestinal region of the duodenum and jejunum, the effect of phosphatidylcholine on this equilibrium was evaluated. The addition of phosphatidylcholine (A) changes the size dimension of the lymphasome formulation (Figure 3B and C), and results in a modest increased recovery of estradiol (Figure 3A). The amount of added phosphatidylcholine that coeluted with the large lymphasomes containing estradiol is shown in Figure 3C.

The optimum recovery of 73% estradiol (Figure 3A) occurs when approximately half of the 0.5 moles of PC coeluted with estradiol (Figure 3C; 0.5 elution pattern). A greater association of PC results in even larger lymphasomes without significant increases in recovery of estradiol.

EXAMPLE 2

It has been demonstrated that estradiol administered p.o. in 20% ethanol/saline to both dogs and monkeys was rapidly and quantitatively absorbed, extensively metabolized by the intestine and liver, and rapidly excreted. A significant amount of estradiol equivalents entered a slow

elimination pool which had a $t_{1/2}$ of 15 to 18 hr. The size of this slow pool being derived from an oral dose was comparable to that being derived from a simultaneously administered intravenous dose. Estradiol administered orally in 20% ethanol/saline yielded more glucuronides than found for estradiol administered in the same control formulation by the intravenous route.

A comparable study was carried out in dogs in which 50 μg of estradiol orally in a lymphasome formulation and 50 μg intravenously in a 20% ethanol/saline solution was simultaneously administered. The results are shown in Figure 4 and Tables 2 and 3. The comparison among the various formulations are summarized in Table 3.

Figure 4 shows the total radiolabeled estradiol equivalents determined in plasma from the jugular and portal veins and in lymph. The concentrations in plasma are initially greater than those found in lymph. Therefore a portion of estradiol in the lymphasome formulation was absorbed rapidly and entered in systemic circulation via the portal vein. This conclusion is supported from the pattern of estradiol and estrone in systemic blood (Figure 4B) and the early appearance (peak) of metabolites in all monitored compartments (Figure 4B, 4C and 4D). The appearance of total radiolabeled equivalents in the lymph was initially less than that observed in portal and systemic plasma but eventually exceed them. A major percentage of the estradiol administered in a lymphasome formulation, co-absorbed with the lipids and entered the systemic circulation via the thoracic lymph.

The cumulative area under each curve in Figure 4 is summarized in Table 2. In all compartments the major fraction represents the glucuronides of estradiol and estrone. Both estrone and estradiol per se represent a small fraction of the total equivalents. These pharmacckinetic parameters for estradiol administered orally in a lymphasome formulation can be compared to similar parameters derived from estradiol administered orally or intravenously in 20% ethanol/saline (Table 3). In brief, the yield of glucuronides from the lymphasome-administered estradiol was less than that found for 20% ethanol/saline by either route and the yield of both estradiol and estrone was greater than that being derived from the orally administered estradiol in 20% ethanol/-saline.

It will be appreciated that while the foregoing disclosure relates to preferred embodiments of the invention effective in xenobiotic delivery composition, it is capable of numerous modifications or alterations which may be made by those skilled in the art without departing from the spirit and scope of the invention as set forth in the appended claims.

TABLE 1

Estimated Composition of the Lymphasome Formulations of Estradiol

	% Composition			% Distribution*			
Oil Formulations	Bile Salts	Fatty Acids	Mono-Glyceride	16:0 Palmitate	18:1 Oleic	18:2 Linoleic	18:3 Linolenic
Coconut Oil[a]	50	35	15	$20/_{12}$	$5/_{2}$	$11/_{15}$	$3/_{5}$
Corn Oil	40	40	20	$11/_{11}$	$38/_{38}$	$52/_{54}$	
Olive Oil	45	38	18	$10/_{10}$	$78/_{78}$	$10/_{10}$	
Peanut Oil	32	48	29	$10/_{8}$	$45/_{45}$	$38/_{50}$	$1/_{1}$
Sesame Seed	ca.25 (14-37)	ca.57 (76-45)	ca.20	$10/_{6}$	$43/_{42}$	$40/_{48}$	
Soybean Oil	40	40	20	$10/_{5}$	$20/_{20}$	$50/_{62}$	$10/_{10}$

* % Distribution of the fatty acid in the fatty acid/monoglyceride fractions

[a] The predominant fatty acids in coconut oil were lauric (12:0) and myristic (14:0). The percent distribution of the fatty acid were 28/38 and 28/24 respectively in the fatty acid/monoglyceride fractions.

TABLE 2

Area Under the Curve for Radioactivity Derived from Estradiol-17β Administered Orally in a Lymphasome Formulation to Dogs

	Cumulative ext., μg/ml x minutes					
Minutes	60	120	240	480	720	1440
Systemic Blood						
Total Equivalents (Plasma)	0.089	0.188	0.308	0.461	0.596	0.923
E_2	0.001	0.002	0.004	0.008	0.012	0.023
E_2G	0.027	0.064	0.107	0.160	0.217	0.344
E_1	0.001	0.002	0.004	0.008	0.012	0.026
E_1G	0.005	0.011	0.022	0.047	0.079	0.139
Portal Blood						
Total Equivalents (Plasma)	0.096	0.199	0.339	0.532	0.675	0.966
E_2	0.001	0.002	0.003	0.005	0.010	0.037
E_2G	0.015	0.053	0.102	0.150	0.194	0.292
E_1	0.004	0.007	0.009	0.012	0.016	0.022
E_1G	0.006	0.015	0.026	0.044	0.066	0.108

TABLE 2 CONTINUED

	Cumulative ext, μg/ml x minutes					
Minutes	60	120	240	480	720	1440
Lymph						
Total Equivalents	0.041	0.173	0.352	0.548	0.669	0.925
E_2	0.001	0.001	0.004	0.008	0.011	0.018
E_2G	0.018	0.065	0.143	0.228	0.283	0.395
E_1	0.001	0.001	0.003	0.006	0.007	0.015
E_1G	0.004	0.014	0.032	0.061	0.087	0.142

TABLE 3

Comparison of Area Under the Curve for Radioactivity Derived From Intravenous and Oral Administration of 17β-Estradiol to Dogs

Route & Formulation	Cummulative ext µg/ml x 1440 minutes IV EtOH-Saline	PO Lymphasome	PO EtOH-Saline	Ratio of IV/PO Lymphasome	IV/PO EtOH-Saline
Systemic Blood					
Total Equivalents (Plasma)	1.402	0.923	1.316	1.52	1.06
E_2	0.076	0.025	0.007	3.04	10.85
E_2C	0.480	0.344	0.852	1.40	0.56
E_1	0.042	0.026	0.010	1.62	4.20
E_1C	0.256	0.139	0.726	1.84	0.35
Portal Blood					
Total Equivalents (Plasma)	1.286	0.966	1.371	1.33	0.94
E_2	0.053	0.037	0.018	1.43	2.94
E_2C	0.449	0.292	N.D.	1.54	--
E_1	0.050	0.022	0.033	2.27	1.52
E_1C	0.127	0.108	N.D.	1.18	--

TABLE 3 CONTINUED

Route & Formulation	Cummulative ext µg/ml x 1440 minutes IV EtOH-Saline	PO Lymphasome	PO EtOH-Saline	Ratio of IV/PO Lymphasome	IV/PO EtOH-Saline
Lymph					
Total Equivalents	0.777	0.925	0.784	0.84	0.99
E_2	0.120	0.018	0.003	6.67	40.00
E_2-3G	0.598	0.395	N.D.	1.51	--
E_1	0.034	0.015	0.007	2.26	4.85
E_1G	0.169	0.142	N.D.	1.19	--

N.D. - Not Determined

What is claimed as new and intended to be covered by Letters Patent is:

1. A xenobiotic delivery composition comprising lipid micellular particles incorporating said xenobiotic the lipid micellular particles comprising a bile acid or the pharmaceutically acceptable salts thereof; a fatty acid; and a monoglyceride.

2. The delivery composition in accordance with claim 1 wherein said lipid micellular particles are from about 40Å to about 100Å in diameter.

3. The delivery composition in accordance with claim 2 wherein the bile acid is selected from the group cholic acid, deoxycholic acid, lithocholic acid, chenodioxycholic acid, 3-hydroxy-7-ketocholanic acid; and the pharmaceutically acceptable salts thereof.

4. The delivery composition in accordance with claim 3 wherein said pharmaceutically acceptable salts are the acid conjugates of said bile acids.

5. The delivery composition in accordance with claim 4 wherein said acid conjugates are glycine or taurine.

6. The delivery composition in accordance with claim 2 wherein said monoglyceride is a monoester of gly-

cerine and a fatty acid of the formula $C_nH_{2n+1}COOH$; $C_nH_{2n-1}COOH$; $C_nH_{2n-3}COOH$; or $C_nH_{2n-5}COOH$ wherein n is an integer of from 9-23.

7. The delivery composition in accordance with claim 6 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid.

8. The delivery composition in accordance with claim 2 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

9. A xenobiotic delivery composition comprising lipid micellular particles incorporating said xenobiotic the lipid micellular particles comprising a bile acid or the pharmaceutically acceptable salts thereof; a fatty acid; and a lipase hydrolyzed triglyceride oil

10. A xenobiotic delivery composition in accordance with claim 9 wherein said lipid micellular particles are from about 40Å to about 100Å in diameter.

11. The xenobiotic delivery composition in accordance with claim 10 wherein said acid conjugates are glycine or taurine.

12. A xenobiotic delivery composition in accordance with claim 11 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

13. A method for delivering and releasing a xenobiotic to a mammalian host requiring said xenobiotic comprising a xenobiotic delivery composition comprising lipid micellular particles incorporating said xenobiotic, the lipid micellular particles comprising a bile acid or the pharmaceutically acceptable salts thereof; a fatty acid; and a monoglyceride.

14. The method in accordance with claim 13 wherein said lipid micellular particles are from about 40Å to about 100Å in diameter.

15. The method in accordance with claim 13 wherein the bile acid is selected from the group cholic acid, deoxycholic acid, lithocholic acid, chenodioxycholic acid, 3-hydroxy-7-ketocholanic acid; and the pharmaceutically acceptable salts thereof.

16. The method in accordance with claim 15 wherein said pharmaceutically acceptable salts are the acid conjugates of said bile acids.

17. The method in accordance with claim 16 wherein said acid conjugates are glycine or taurine.

18. The method in accordance with claim 13 wherein said monoglyceride is a monoester of glycerine and a fatty acid of the formula $C_nH_{2n+1}COOH$; $C_nH_{2n-1}COOH$; $C_nH_{2n-3}COOH$; or $C_nH_{2n-5}COOH$ wherein n is an integer of from 9-23.

19. The method in accordance with claim 11 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid.

20. The method in accordance with claim 13 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

21. A method for delivering and releasing a xenobiotic to a mammalian host requiring said xenobiotic comprising lipid micellular particles incorporating said xenobiotic, the lipid micellular particles comprising a bile acid or the pharmaceutically acceptable salts thereof; a fatty acid; and a lipase hydrolyzed triglyceride oil.

22. The method in accordance with claim 21 wherein said lipid micellular particles are from about 1COA in diameter.

23. The method in accordance with claim 22 wherein said acid conjugates are glycine or taurine.

24. The method in accordance with claim 22 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

25. The method in accordance with claim 22 wherein said monoglyceride is a monoester of glycerine and a fatty acid of the formula $C_nH_{2n+1}COOH$; $C_nH_{2n-1}COOH$; $C_nH_{2n-3}COOH$; or $C_nH_{2n-5}COOH$ wherein n is an integer of from 9-23.

26. The method in accordance with claim 25 wherein said fatty acid is selected from the group myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid.

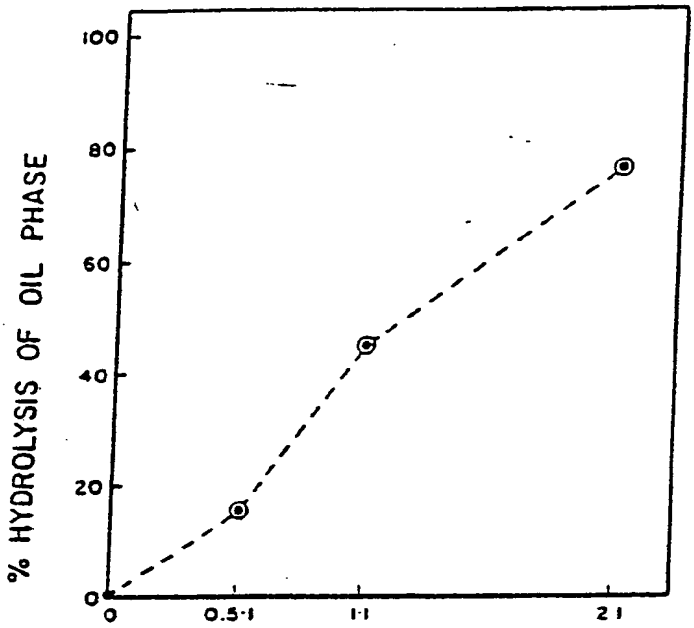


FIG. 1A

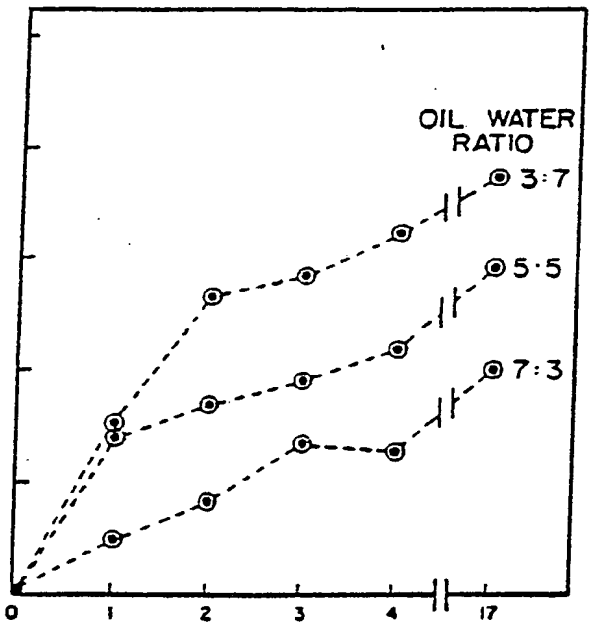


FIG. 1B

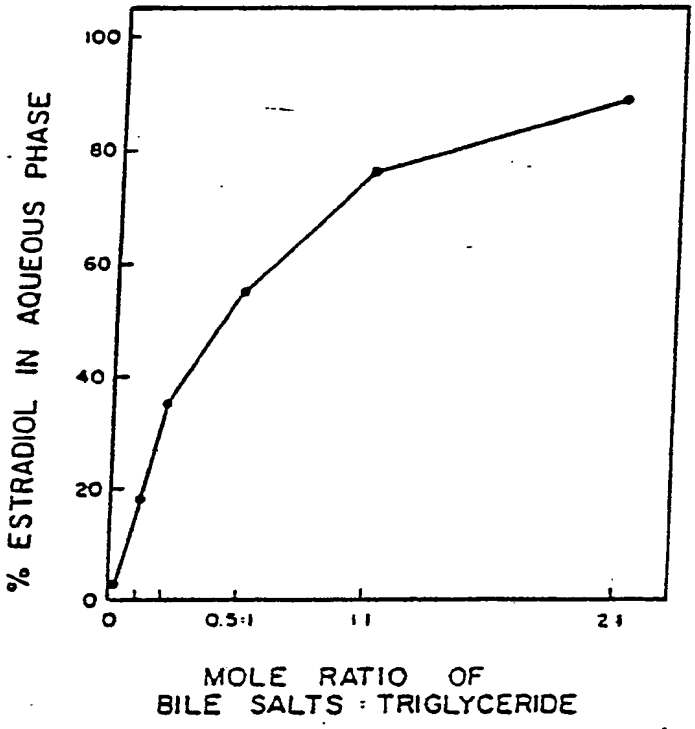
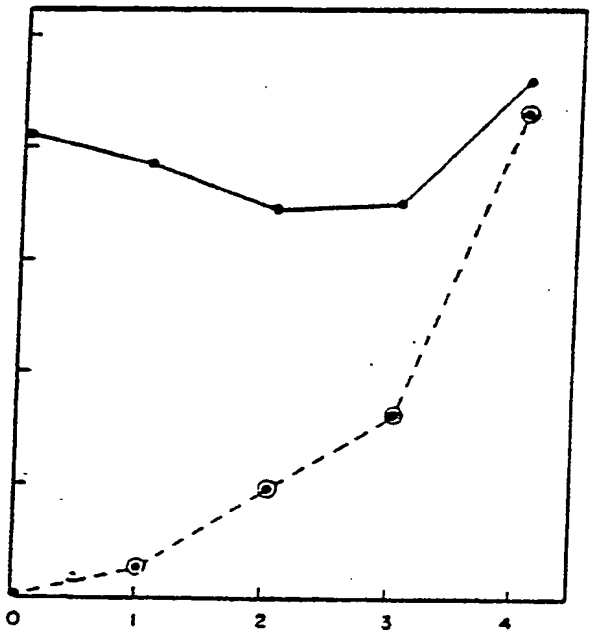


FIG. IC



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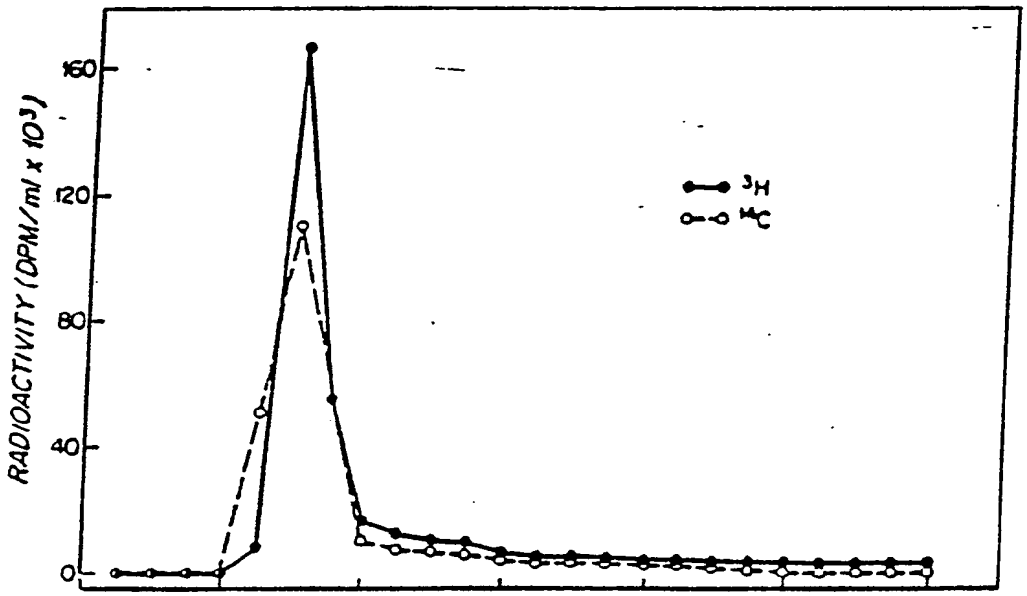


FIG. 2A

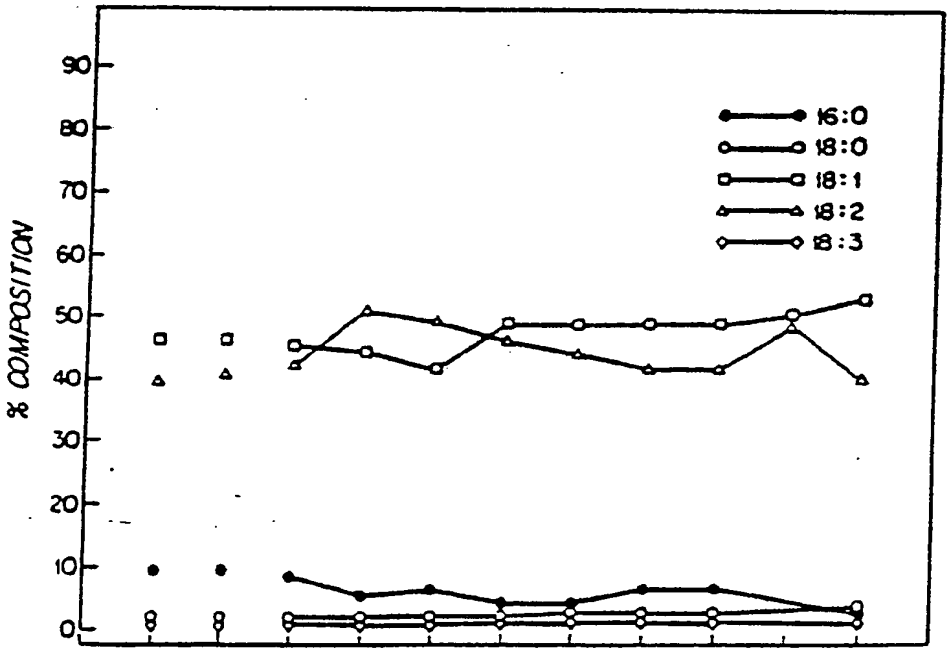


FIG. 2B

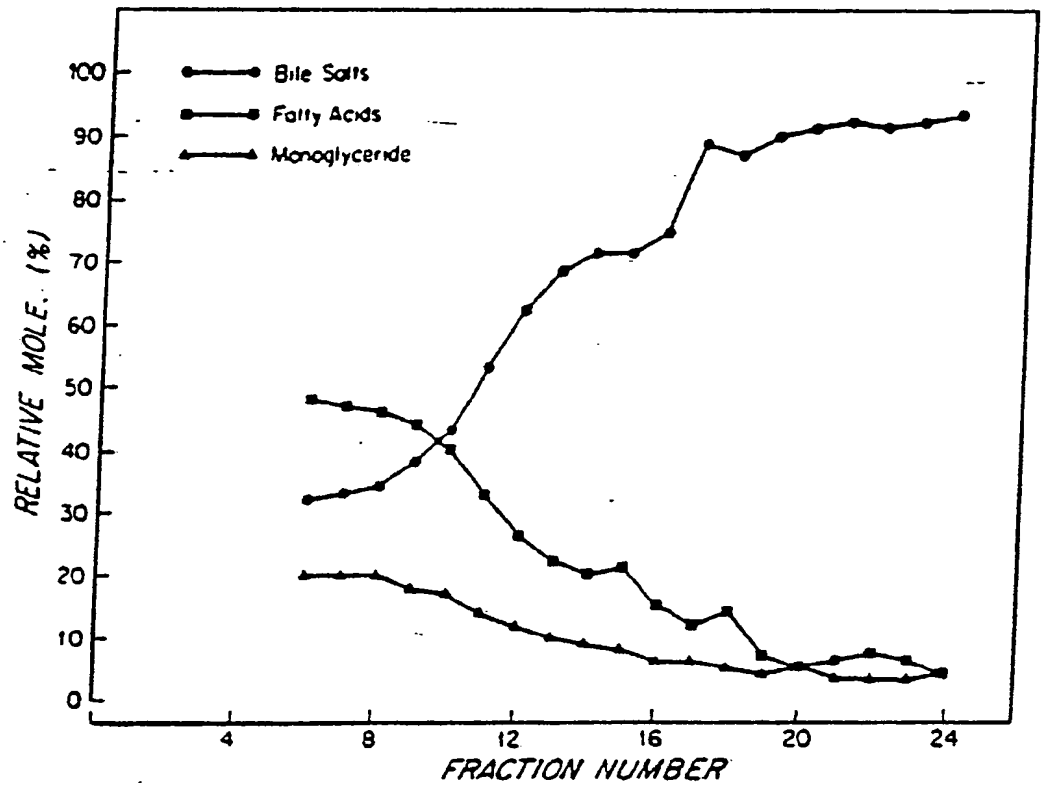


FIG. 2C

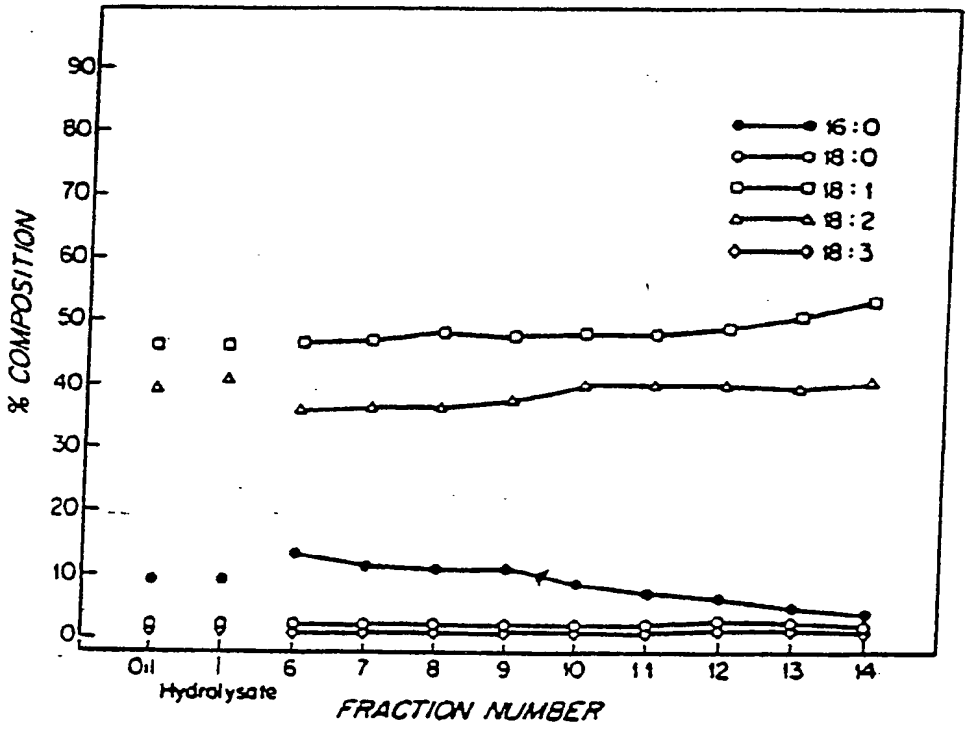


FIG. 2D

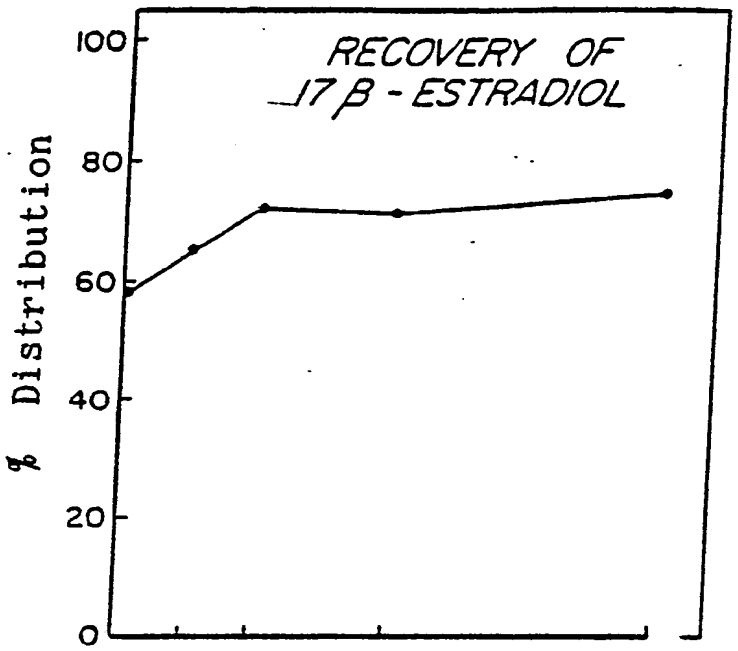


FIG. 3A

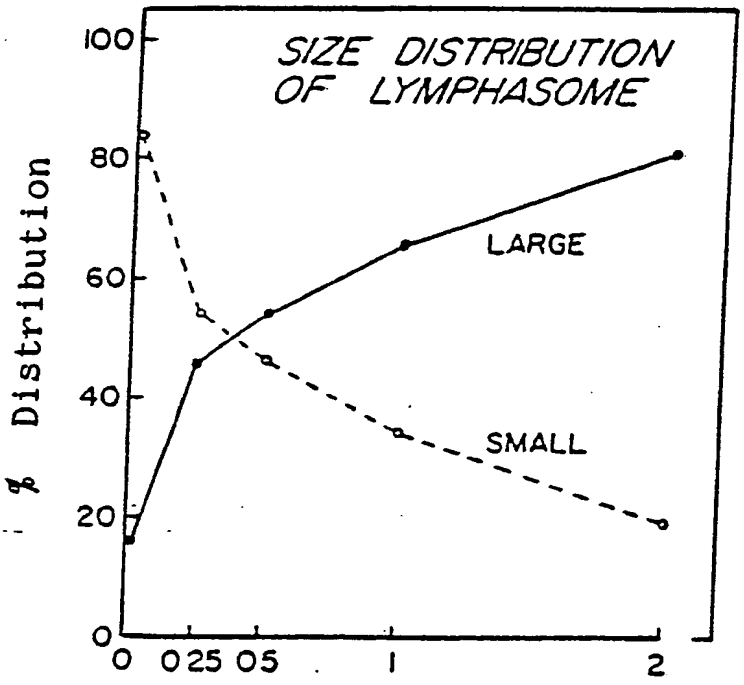


FIG. 3B

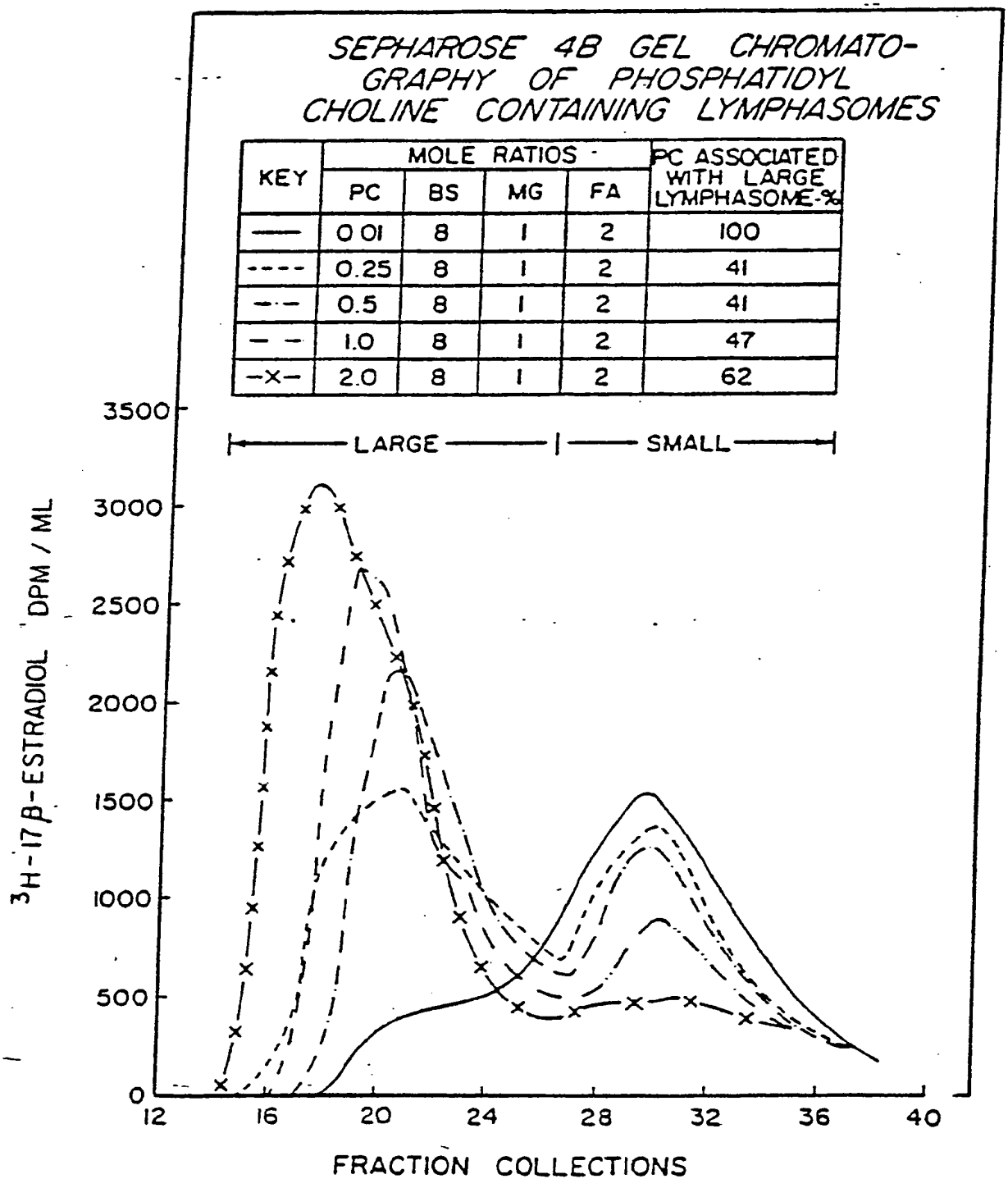
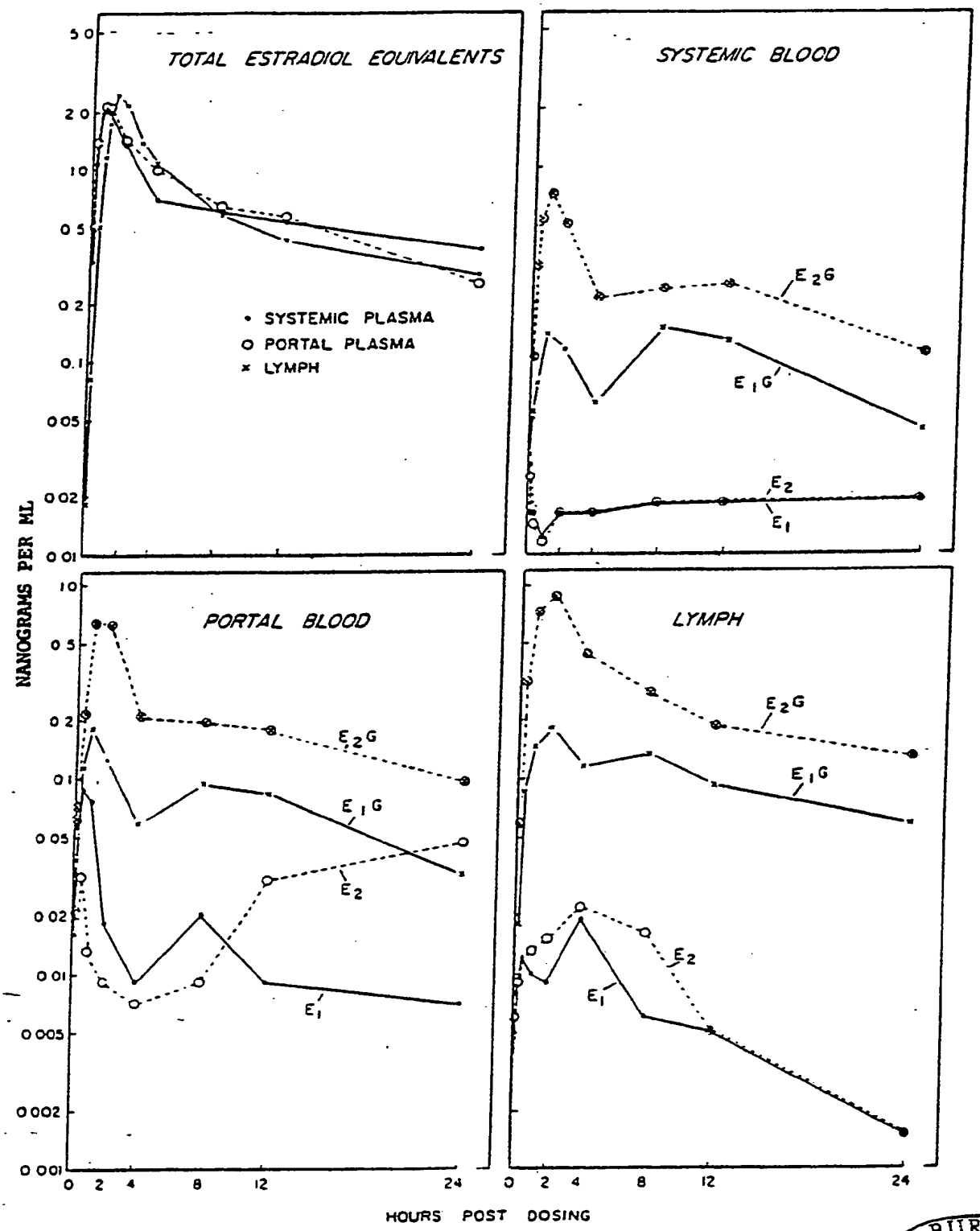


FIG. 3C

FIG. 4A

FIG. 4B



INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00932

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. Cl.[3] B01J 13/02; A61K 9/50, 9/52.
US Cl. 252/316;424/19,38

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	252/316;424/19,38

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,115,313, Published 19 September 1978 Lyon et al.	1-26
A	US, A, 4,217,344, Published 12 August 1980, Vanlerberghe et al.	1-26
A	N, The New England Journal of Medicine, Vol. 295, No. 13, issued 23 September 1976 See pages 704-710.	1-26

* Special categories of cited documents: [19]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
25 October 1982	29 OCT 1982

International Searching Authority [1]

ISA/US

Richard D. Lovering
Primary Examiner